Prevalence of Esophageal Atresia among 18 International Birth Defects Surveillance Programs

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Abstract

BACKGROUND—The prevalence of esophageal atresia (EA) has been shown to vary across different geographical settings. Investigation of geographical differences may provide an insight into the underlying etiology of EA.

METHODS—The study population comprised infants diagnosed with EA during 1998 to 2007 from 18 of the 46 birth defects surveillance programs, members of the International Clearinghouse for Birth Defects Surveillance and Research. Total prevalence per 10,000 births for EA was defined as the total number of cases in live births, stillbirths, and elective termination of pregnancy for fetal anomaly (ETOPFA) divided by the total number of all births in the population.

RESULTS—Among the participating programs, a total of 2943 cases of EA were diagnosed with an average prevalence of 2.44 (95% confidence interval [CI], 2.35–2.53) per 10,000 births, ranging between 1.77 and 3.68 per 10,000 births. Of all infants diagnosed with EA, 2761 (93.8%) were live births, 82 (2.8%) stillbirths, 89 (3.0%) ETOPFA, and 11 (0.4%) had unknown outcomes. The majority of cases (2020, 68.6%), had a reported EA with fistula, 749 (25.5%) were without fistula, and 174 (5.9%) were registered with an unspecified code.

CONCLUSIONS—On average, EA affected 1 in 4099 births (95% CI, 1 in 3954–4251 births) with prevalence varying across different geographical settings, but relatively consistent over time and comparable between surveillance programs. Findings suggest that differences in the prevalence observed among programs are likely to be attributable to variability in population ethnic compositions or issues in reporting or registration procedures of EA, rather than a real risk occurrence difference.

Keywords

esophageal atresia; congenital anomalies; prevalence; epidemiology

INTRODUCTION

Esophageal atresia (EA) is the most frequent anomaly of the esophagus and is characterized by the complete discontinuity of the esophagus with or without an abnormal connection between the esophagus and the trachea—tracheo-esophageal fistula (TEF). Diagnosis occurs prenatally or, in most cases, at birth and surgical repair is required in the first few days of life. Although the etiology of EA is largely unknown (Felix et al., 2009), geographic, temporal, and ethnic variations have been reported.

The prevalence of EA has been shown to vary across and within different geographical settings with a study from five regions in Britain reporting estimates ranging between 0.7 and 3.2 per 10,000 births (Rankin et al., 2005), although EA cases in that study also included

those with esophageal stenosis. Similarly, differences in rates among areas in the United States have been reported with a prevalence of 2.24 in Hawaii (Forrester and Merz, 2005), 2.33 in Texas (Ethen and Canfield, 2002), and 2.82 per 10,000 births in California (Torfs et al., 1995); among European countries, prevalence has been reported for Iceland (1.83 per 10,000; Gunnarsdottir et al., 2004), Strasbourg, France (2.96 per 10,000; Stoll et al., 2009), and the United Kingdom Northern Region (3.13 per 10,000 births; Sparey et al., 2000). Given that EA is a rare condition, small numbers may also have a potential effect on rates. Ethnic composition of a population may also influence EA prevalence, with lower rates noted among Hispanic and African American communities (Carmichael et al., 2004; Forrester and Merz, 2005).

International differences in the prevalence of EA across different geographical regions may also be attributable to differences in case identification methods, case definition, and case ascertainment.

Best estimates of prevalence of major birth defects, based on international data, are important to serve as a reference point for the evaluation of individual, regional, or national surveillance programs and to identify geographical regions of higher or lower than expected prevalence (Leoncini et al., 2008; Cocchi et al., 2010). Investigation of geographical differences may also provide an insight into the underlying etiology of EA. The aim of this study was to investigate the international prevalence of EA among birth defects surveillance programs in North and South America, Europe, and Australia and provide a worldwide collective estimate.

MATERIALS AND METHODS

Data for this study were sourced from 18 birth defects surveillance programs, all members of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR). Programs who agreed to participate provided relevant data on EA among live births, stillbirths, and elective termination of pregnancy for fetal anomaly (ETOPFA), if permitted. All participating programs were also required to have a stable methodology of ascertainment and registration over the 10-year study period of 1998 to 2007. The following programs provided data for slightly different years: Slovak Republic, 2001 to 2007; Texas, 1997 to 2006; and Utah, 1999 to 2007.

The main characteristics of the 18 participating programs in this study are reported in Table 1, with additional details available from the annual reports of the ICBDSR (http://www.icbdsr.org; International Clearing-house for Birth Defects Surveillance and Research, 2008) and the National Birth Defects Prevention Network (http://www.nbdpn.org; National Birth Defects Prevention Network, 2008), and from selected publications from individual programs (Mutchinick et al., 1988; Czeizel, 1997; Correa-Villasenor et al., 2003; Castilla and Orioli, 2004; De Vigan et al., 2005; Feldkamp et al., 2005; Bower et al., 2009; Lowry RB et al., 2009).

Classification of cases was undertaken by each individual program using either the British Pediatric Association International Classification of Diseases (ICD) coding system (ICD9-

BPA) or ICD10. For this study, EA cases included all reported infants and fetuses diagnosed with an esophageal atresia with TEF (ICD9-BPA: 750.31, 750.33; ICD10: Q39.1) or without TEF (ICD9-BPA: 750.30; ICD10: Q39.0) or unspecified EA (750.3). Other types of EA including TEF without atresia (ICD9-BPA: 750.32; ICD10: Q39.2), esophageal stenosis, or esophageal web (ICD9-BPA: 750.34, 750.35; ICD10: Q39.3, Q39.4) were considered separately.

Total prevalence per 10,000 births was defined as the total number of cases among live births, stillbirths, and ETOPFA divided by the total number of all births (live births and stillbirths) in the population. Spontaneous abortions were not considered. We used the term *total prevalence* instead of *prevalence* or *birth prevalence* to underline that ETOPFA was also included. To validate the total prevalence, we undertook a sensitivity analysis by comparing overall total prevalence to estimated result for six programs previously shown to have good ascertainment of birth defects (Leoncini et al., 2010). Ninety-five percent confidence intervals (CIs) for prevalence were calculated based on the Poisson distribution. Chi-square test for trend was used to evaluate homogeneity and time trend of the prevalence in the study period. Statistical analyses were performed using Stata 9.0 (Stata Corporation, College Station, TX) and SAS 9.1 (SAS Institute, Cary, NC), with $p < 0.05$ considered statistically significant.

RESULTS

Among the eighteen surveillance programs of the ICBDSR, a total of 2943 cases of EA were registered between 1998 and 2007 (Table 2). The majority of cases (2020, 68.6%) had a reported esophageal atresia with fistula, 749 cases (25.5%) were without fistula, and 174 cases (5.9%) were unspecified. The total prevalence of EA was 2.44 (95% CI, 2.35–2.53) per 10,000 births; and on average, EA affected 1 in 4099 births (95% CI, 3954–4251 births). The prevalence ranged from 1.77 (95% CI, 1.52–2.06) per 10,000 births in Hungary and Atlanta to 3.68 (95% CI, 3.41–3.97) in South America (Table 2). Sensitivity analysis using data from programs with optimal ascertainment of cases revealed that total prevalence of EA was 2.47 per 10,000 births.

Overall, the average annual trend in EA remained fairly constant over the study period varying between 2.32 in 1998 to 2.60 per 10,000 births in 2007, and there was no evidence of a significant linear trend in EA among each of the programs (data not shown). However, there was a modest decline in the trend of EA in Alberta and Dublin, and a slight increase in cases in Western Australia, Mexico, and Israel.

Of all infants with a diagnosis of EA, there were 2761 (93.8%) live births, 82 (2.8%) stillbirths, 89 (3.0%) ETOP-FAs, and 11 (0.4%) with unspecified outcome. Programs in Dublin and Alberta had a relatively higher proportion of stillbirths (14.0% and 11.4%, respectively); in the case of ETOPFA, two programs (i.e., Central East, France and Wales) reported one in five cases that resulted in a termination of pregnancy (Fig. 1). Excluding ETOPFA, the total prevalence of EA reduced slightly to 2.37 (95% CI, 2.28–2.45) per 10,000 births.

The total prevalence of TEF without atresia was 0.22 per 10,000 births (95% CI, 0.19–0.24; 1 in every 46,398 births). Compared with EA, TEF without atresia was reported much less frequently (<0.5 per 10,000 births) by all members of ICBDSR except for Western Australia, where the prevalence was 1.3 per 10,000 births. Cases of esophageal stenosis or esophageal web (n = 44) occurred rarely, 1 in every 274,170 births (0.04 per 10,000 births), but was more commonly diagnosed in Saxony–Anhalt, Germany (0.12 per 10,000 births) compared with all other surveillance programs.

DISCUSSION

Esophageal atresia affects an average of 1 in every 4099 births, with a total prevalence of 2.44 (95% CI, 2.35–2.53) per 10,000 births among 18 birth defects surveillance program members of the ICBDSR. The prevalence ranged between 1.77 and 3.68 per 10,000 births among members representing North and South America, Europe, and Australia. However, sensitivity analysis limiting data to member programs with optimal case ascertainment revealed an almost identical total prevalence (2.47). The findings are also similar to an earlier study of EA among nine ICBDSR programs reporting a prevalence of 2.56 per 10,000 births from 1965 to 1989 (Robert et al., 1993).

Findings from other congenital anomaly surveillance programs such as EUROCAT (the European surveillance of congenital anomalies working group) reported a comparable prevalence of 2.46 per 10,000 births among 23 member registries for the years 1997 to 2006 (Pedersen et al., 2012). This analysis included five ICBDSR members from our present study. When limiting our data to 10 European members of the ICBDSR, we also found the same result (2.44 per 10,000 births). The estimated national prevalence of EA reported by the U.S. National Birth Defects Prevention Network was 2.12 per 10,000 births (adjusted for race or ethnicity) among 14 member programs for the period from 2004 to 2006. Slight differences in prevalence by case ascertainment methods were observed with results ranging from 2.17 among 10 programs using active birth defects surveillance to 2.36 among seven passive surveillance systems and 2.54 among five passive surveillance programs with a case confirmation component (Parker et al., 2010).

Despite the range of geographic locations and study periods, comparison of the total prevalence of EA by various international surveillance programs reveals relatively similar results with EA diagnosed among 1 in 4099 to 4608 infants. These findings highlight the relative stability of the prevalence of EA, internationally and over time. In our international study, there was no consistent trend for neighboring countries or states within continents, with a small variability in prevalence potentially influenced by chance or differences in reporting or surveillance methods, study population, ethnic distribution, or geographical or environmental factors. For example, the two programs reporting higher prevalence of EA (South America and Israel) may be explained by their hospital-based case ascertainment program with active notification by trained clinicians in each hospital. However, higher prevalence may also reflect a truly higher rate of EA, and further investigation of these results is important. Conversely, slightly lower prevalence of EA reported from surveillance programs in Atlanta and Texas may be explained by the ethnic composition of the population in these two U.S. states, with almost two thirds of all infants born to African

American or Hispanic women, respectively (National Birth Defects Prevention Network, 2009). Studies of congenital malformations by ethnic groups in the United States have found that compared with non-Hispanic white women, Hispanic and African American women had a reduced risk of EA without fistula (relative risk, 0.75; 95% CI, 0.62–0.90; and relative risk, 0.59; 95% CI, 0.62–0.90; respectively; Carmichael et al., 2004; Forrester and Merz, 2005). In Hungary, a combination of incomplete registration of cases at birth and terminations of pregnancy, and a true lower prevalence may explain their lower estimates.

Although there was some discrepancy among programs in the distribution of specific types of EA (with and without TEF), the overall proportions were similar to those reported in the literature (Clark, 1999; Shaw-Smith, 2006; Spitz, 2007). These differences may be due to variation in classification, identification, or reporting practices across programs rather than reflect real differences (Shaw-Smith, 2006; Spitz, 2007). Higher prevalence of TEF without atresia in some settings may also be due to increased detection and sources of notification such as post mortem evaluation (Bower et al., 2009). Several factors may also influence reporting and registration of EA including: screening policies and procedures, clinician skills, timing of aneuploidy and fetal anomaly screening, subsequent availability and timing of elective termination of pregnancy, and autopsy policies. Previous studies have shown that the rate of termination of pregnancy is higher for cases with chromosomal or additional congenital anomalies than for cases with an isolated anomaly (Haeusler et al., 2002; Garne et al., 2007). Chromosomal anomalies have been reported to occur in 6 to 10% of EA cases (Garne et al., 2007; Genevieve et al., 2007; Pedersen et al., 2012); while greater than 50% and up to two thirds of infants with EA have additional anomalies (Genevieve et al., 2007; Spitz, 2007; de Jong et al., 2010a; Pedersen et al., 2012). Given that EA is more likely to be diagnosed in conjunction with other syndromes (particularly VACTERL: Vertebral anomalies, Anal atresia, Cardiovascular anomalies, Tracheo-Esophageal fistula, Renal and/or Radial anomalies, Limb defects) or chromosomal anomalies that may result in termination of pregnancy, it is important to include terminated cases in ascertainment (Shaw-Smith, 2006; Felix et al., 2009). For some anomalies, availability and reporting of ETOPFA may increase ascertainment of cases. In this study, total prevalence of EA was only slightly attenuated to 2.37 per 10,000 births if terminations were excluded. This finding was confirmed by a study from Texas that found no effect on estimates of EA when elective terminations before 20 weeks' gestation were included in case ascertainment (Ethen and Canfield, 2002).

The underlying etiology of EA has been described as multifactorial and is likely to differ across settings (Robert et al., 1993; Felix et al., 2009; de Jong et al., 2010b). In addition to maternal ethnicity and geographic location, previous studies have reported EA to be associated with maternal age (Leck et al., 1968; Harris et al., 1995), multiple gestation (Harris et al., 1995; Riley et al., 1998), infant sex (Robert et al., 1993) and use of assisted reproductive technology (Reefhuis et al., 2009). In a recent study of EA in the United States, women using assisted reproductive technology had a 4.5-fold increased risk of having an infant with EA (Reefhuis et al., 2009). Prevalence of EA has also been found to be higher among multiple births compared with singletons (Harris et al., 1995; Riley et al., 1998), and increased risk was reported with increasing maternal age (Leck et al., 1968; Harris et al., 1995). In contrast, a protective effect was found among women who have had three or more

births (OR, 0.50; 95% CI, 0.36–0.71; Harris et al., 1995; Carmichael et al., 2004). However, given the low frequency of occurrence of most of these factors in the general population, the population-attributable risk is likely to be minimal. Variations in ethnicity as detailed above may also be surrogates for a number of different exposures, including socioeconomic status, nutrition, stress, and access to services. Differences in lifestyle factors, such as smoking or dietary habits within countries or regional variation, may also affect estimates. However, lack of temporal trends among the included programs suggests environmental factors, which change over time, are less likely to play a role in the development of EA (Robert et al., 1993; Canfield et al., 2006; Garne et al., 2007). Underlying and still unknown (Genevieve et al., 2011) genetic susceptibility, biologic or physical differences may also modify risk of exposures. Although a number of genetic abnormalities have been associated with EA, no specific gene has been implicated (Felix et al., 2009). Further study with more detailed information to assess risk factors and underlying characteristics of cases with EA is required.

One of the limitations of the study is that it did not collect information on maternal risk factors that might help to elucidate the etiology of EA or explain differences in the prevalence across settings. Furthermore, we did not collect information to differentiate between isolated cases and those with associated (multiple) or chromosomal anomalies because of difficulties in standardizing the definition of associated anomalies across programs. Despite these limitations, one of the strengths of the study is that case identification is likely to be complete because EA is diagnosable either antenatally or at the time of birth and require surgical attention. Recent studies from the Netherlands and Oxford, U.K., reported that diagnosis of EA occurred prenatally in 38% of infants (Choudhry et al., 2007; Garne et al., 2007; de Jong et al., 2010a; Pedersen et al., 2012). Postnatally, EAs are suspected and diagnosed by respiratory or feeding difficulties and inability to pass a nasogastric tube; they are confirmed on chest radiograph with surgical correction within 24 to 48 hours (Spitz, 2007).

In conclusion, EA affects an average of 1 in every 4099 births worldwide and has remained surprisingly stable over time. Although there was some variation in the reported prevalence among and within countries, overall EA was also relatively consistent across European and American surveillance programs. Findings suggest that differences in the prevalences observed among programs are likely to be attributable to local phenomena affecting reporting or case registration of EA or ethnic composition, rather than a real difference in risk occurrence per se. Future epidemiologic studies accounting for ethnic distribution, maternal characteristics, genetic factors, and associated anomalies may provide important information regarding the underlying epidemiology of EA.

Acknowledgments

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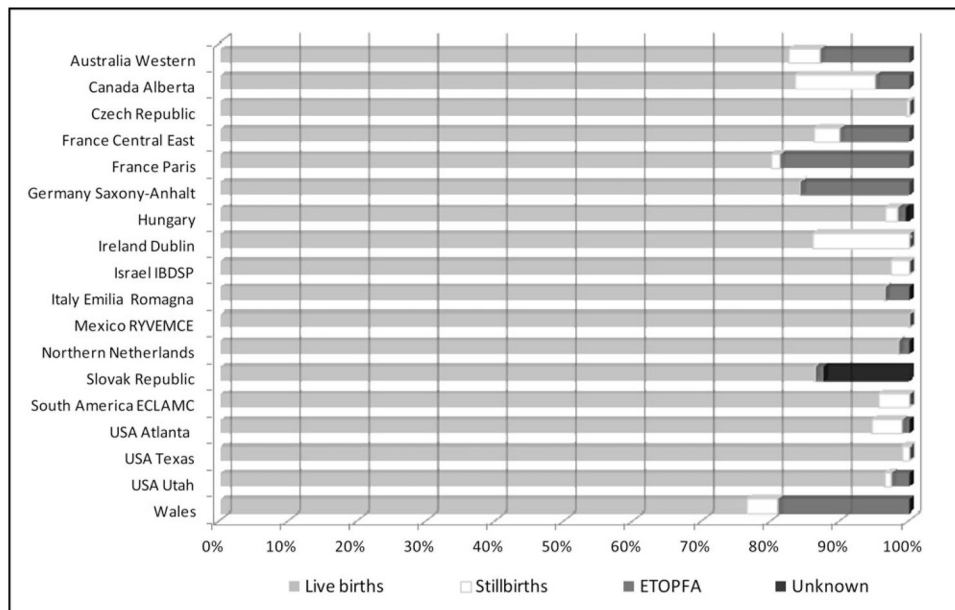
ETOPFA = elective termination of pregnancy for fetal anomaly

Figure 1.
Proportion of esophageal atresia among eighteen surveillance program members of the International Clearinghouse for Birth Defects Surveillance and Research, by pregnancy outcome, 1998–2007.

Table 1

Characteristics of 18 Surveillance Programs of the International Clearinghouse for Birth Defects Surveillance and Research Reporting on Esophageal Atresia

Surveillance programs	Coverage	ETOPFA	Maximum age or source of ascertainment or registration	Source of ascertainment of live births, stillbirths and ETOPFA	Criteria defining stillbirths
Australia Western Australia	PP1	P, R	6 years	M	20 weeks or 400 g
Alberta, Canada	RP	P, R	1 year	M	20 weeks or 500 g
Czech Republic	RP	P, R	15 years	M	28 weeks or 1000 g
Paris, France	PP1	P, R	Hospital discharge	M	22 weeks
France, Central East	RP	P, R	18 months	M	22 weeks
Germany Saxony–Anhalt	PP2	P, R	1 year	M	500 g
Hungary	RP	P, R	1 year	M	24 weeks or 500 g
Dublin, Ireland	RP	NP	5 years	M	24 weeks or 500 g
Israel	H	P, R	3–7 days	S	20 weeks or 500 g
Emilia Romagna, Italy	PP1	P, R	1 week	S	180 days
Mexico	H	NP	Hospital discharge	S	20 weeks or 500 g
Northern Netherlands	RP	P, R	15 years	M	24 weeks
Slovak Republic	PP1	P, R	1 year	S	28 weeks or 1000 g
South America	H	NP	Hospital Discharge	S	500 g
Atlanta, Georgia	RP	P, R	6 years	M	20 weeks
Texas	RP	P, R	1 year	M	20 weeks[a]
Utah	RP	P, R	5 years	M	20 weeks
Wales	RP	P, R	1 year	M	24 weeks

[a]Before 2001, 20 weeks. Since 2001, all stillbirths with documented birth defects included.

ETOPFA, elective terminations of pregnancy for a fetal anomaly; P, permitted by country's laws; R, reported; M, multiple sources; RP, resident population (includes only cases born to mothers residing in the area covered by the registry during pregnancy, despite where the delivery took place, and excluding all cases born to nonresident mothers who delivered in the area covered by the registry); PP1, present population, including all cases born to mothers who delivered in the area covered by the registry, regardless of where they were residing during pregnancy (the registry does not cover cases born outside the area, even if the mother is resident in the area); PP2, present population, excluding subjects born to mothers who delivered in the area covered by the registry but were residing out of the area (the registry does not cover cases born outside the area even if the mother is residing in the area); NP, not permitted; H, hospital-based (includes only a proportion, even near to 99%, of all subjects delivered in the area covered by the registry); S, single source.

Table 2

Prevalence of Esophageal Atresia among 18 Surveillance Programs of the International Clearinghouse for Birth Defects Surveillance and Research, 1998–2007, by Increasing Prevalence

Surveillance program	Total births	EA with TEF	EA without TEF	Unspecified atresia, fistula or stenosis	Total cases	Prevalence (per 10,000 births)	95% CI	
Hungary	970,828	25	147	0	172	1.77	1.52	2.06
Atlanta, Georgia[a]	513,272	71	20	0	91	1.77	1.43	2.18
Texas[a,b]	3,305,512	495	102	0	597	1.81	1.66	1.96
Alberta, Canada	404,595	66	13	0	79	1.95	1.55	2.43
Slovak Republic[b]	371,644	45	35	0	80	2.15	1.71	2.68
Paris, France	363,914	72	8	0	80	2.20	1.74	2.74
Germany Saxony–Anhalt	162,723	24	14	0	38	2.34	1.65	3.21
Utah[b]	453,129	100	11	0	111	2.45	2.02	2.95
Dublin, Ireland	227,586	55	2	0	57	2.50	1.90	3.24
Czech Republic	969,144	169	82	0	251	2.59	2.28	2.93
Western Australia	262,338	65	4	0	69	2.63	2.05	3.33
Mexico	264,415	31	41	0	72	2.72	2.13	3.43
Wales	323,462	78	11	0	89	2.75	2.21	3.39
France, Central East	956,012	137	130	0	267	2.79	2.47	3.15
Emilia Romagna, Italy	288,155	64	17	2	83	2.88	2.29	3.57
Northern Netherlands	195,100	49	12	1	62	3.18	2.44	4.07
Israel	208,782	0	0	74	74	3.54	2.78	4.45
South America	1,822,848	474	100	97	671	3.68	3.41	3.97
Total	12,063,459	2,020	749	174	2,943	2.44	2.35	2.53

[a] Includes a few cases of possible or probable diagnosed cases.

[b] Years available: Slovak Republic, 2001–2007; Utah, 1999–2007; Texas, 1998–2006.

EA, esophageal atresia; TEF, tracheo-esophageal fistula.

EA with TEF (ICD9-BPA: 750.31, 750.33; ICD10: Q39.1); EA without TEF (ICD9-BPA: 750.30; ICD10: Q39.0); unspecified atresia, fistula or stenosis (ICD9-BPA: 750.3; no corresponding ICD10 codes).